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Genetics and the Dead: Implications for Genetics Research With Samples From Deceased Persons

Evan G. DeRenzo,[1]* Leslie G. Biesecker,[2] and Noah Meltzer[2]
[1]*Department of Clinical Bioethics, National Institutes of Health, Bethesda, Maryland*
[2]*National Center for Human Genome Research, Bethesda, Maryland*

Recent technological advances in molecular genetics research allow studies of genomic alterations on minute samples of tissue, including tissue from deceased persons. Several highly publicized reports in which these techniques have been applied to famous deceased persons, such as Abraham Lincoln, Toulouse-Lautrec, and the Romanov family [Ranum et al., 1994; Gill et al., 1994; Frey, 1995], have already appeared. These technological advances raise new questions about the definition of human subjects. Scientific advances require us to think beyond the individual subject to consider risks to the family group. There is a growing appreciation of an expansion of potential risks and a blurring of the distinction between tissue from living and deceased persons. These complexities require thoughtful interpretation of the Federal regulations [45 CFR 46 1991] governing the ethical conduct of human subjects research.

Currently, review of research studies involving tissue from persons who were dead before study, or from whom tissue was collected after death, is different than review of research studies involving specimens from living persons. Studies involving samples from dead persons are not considered to come under the purview of the regulations on human subjects research, the Code of Federal Regulations (CFR) [45 CFR 46 1996]. The phrase "specimens from dead persons" or "research involving dead persons" shall herein be understood to be research on samples from persons who died after collection of the specimen or from whom the tissue was collected after death. This exclusion results from the definition of the term "human subject" in the federal regulations, 45 CFR 46.102(f) [45 CFR 46 1996]. This interpretation derives from the definition of human subject as "a living individual about whom an investigator . . . conducting research obtains (1) data . . . or (2) identifiable private information." This definition of human subject is used throughout the CFR. The rules in section 46.101(a) specify that "this policy applies to all research involving human subjects . . . ." Because of the definition of human subject as a living person, research involving samples from dead persons has not been covered by the regulations. Because the definition focuses on the individual, an awareness that in genetics research the family is the subject has been slow to emerge.

The spirit of the regulations is to protect persons from potential harm produced in the research setting. In spite of this intent, research with tissue from deceased persons is not covered by current regulatory criteria. Study of specimens from dead persons can produce results that have direct implications for living persons, that is, the living relatives of the deceased from whom the samples came. Molecular genetic research on samples from deceased persons is one area in which the current regulations fail to address the potential risks faced by living relatives [Billings et al., 1992; Capron 1993; American Society of Human Genetics 1995; Clayton-Wright et al., 1995; Juengst, in press]. The failure of these regulations to address such possibilities is illustrated by the following case examples.

Case 1

A 26-year-old woman presents for participation in a genetic testing research protocol on familial breast cancer. Her mother was diagnosed with breast cancer in her fifth decade and is currently ill with metastatic disease. The maternal grandmother and aunt have also had breast cancer onset prior to age 50. The proband has several brothers. The proband and her biologic family are at odds about breast cancer genetic testing. The proband is considering prophylactic mastectomy and wants to be tested to learn her risk for familial breast cancer. In order to test the proband, it is necessary to have a specimen from an affected relative. The rest of the family is opposed to genetic testing and denies any possibility that she could be at risk because of a familial predisposition. The proband elects to delay her own testing until after her mother's death. She plans to then request directly from her mother's treating physicians access to her deceased mother's tissue blocks to allow determination of the causative mutation.

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*Correspondence to: Evan G. DeRenzo, Ph.D., National Institutes of Health, Department of Clinical Bioethics, Building 10 Room 1C116, Bethesda, MD 20892-1154. Email: derenzo@nih.gov.

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Case 2

Now that genetic mutations for some forms of breast cancer have been identified, John Smith, MD, a researcher at the University of the Midwest Medical School wants to conduct an epidemiologic study searching for a particular mutation. There is a registry to which he has been granted access. Tissue in the registry is from persons who have died of breast, colon, or uterine cancer. He is concerned about what he should do about reporting results back to living relatives who may be at risk for carrying the same mutation or whether he should make the samples anonymous.

These cases illustrate the complexities created by the exclusion from regulatory oversight of tissue from deceased persons, in addition to other clinical ethics issues. We focus in this article on the issues surrounding the use of tissue from deceased persons. If these studies were covered by the regulations, the Institutional Review Board (IRB) would have had to struggle with many questions. Some raised by the first case include how to weigh the mother's refusal to provide the tissue and about the risks to other relatives posed by information gained on behalf of the proband. A question central to the second is, what are the duties and obligations of researchers to living persons about whom clinically relevant information is generated when those persons are not voluntary participants in the research?

These cases demonstrate the flaw in the assumption that research on specimens from deceased persons is without risk to living persons. Genetic research on samples obtained from deceased individuals can have consequences for relatives similar to those seen in research conducted with samples from living persons. Risks may be similar, regardless of the source of the study samples. If the use of samples from deceased persons is not included in protocol review, there may be little or no consideration of the impact of the research on the living relatives. The relatives of the deceased may not be given the choice to be exposed to information gained in the study. It is likely that relatives of the deceased will not have given their consent to incur the risks posed to them by possible breaches of confidentiality and intrusions on their privacy. Genetic counseling obligations may be overlooked. Review can minimize these potential harms.

In case 1, it is easy to imagine that the proband's brothers would be upset with her for obtaining her deceased mother's tissues for the purpose of genetic testing. The use of her mother's tissue to make a diagnosis of familial breast cancer could disrupt the coping mechanisms of other relatives. Information gained may pose psychological risks as well as practical ones. Threats to insurability and employability are raised for relatives when genetic research is performed on their deceased relatives' tissue and disease predispositions are determined. Case 2 has the potential for creating a broad spectrum of risks for persons who not only did not consent to be involved in a research study but who would not even know that the information about them was being generated or stored.

More broadly, individuals who feel they were excluded from, or included in, a research study against their will and/or without their knowledge, especially when the research produces sensitive information, may exhibit anger toward, or mistrust in, the research enterprise. Under present regulatory requirements, these research-related risks could be incurred by living individuals in the absence of any human subjects review. With adequate prospective review and consideration, some of these risks can be minimized or avoided by using strategies now applied to genetics research requiring review [e.g., MacKay, 1993; OPRR, 1993].

There are two ways this situation can be addressed. The first is to amend the federal regulations for human subjects research. However, regulatory change is a slow and laborious process. The second, more practical, approach is to interpret the regulations broadly. Thoughtful interpretation can correct this omission and may avoid a lengthy and cumbersome process of regulatory alteration. Toward that end we suggest that investigators reconceptualize "the family" as the "subject" requiring protection and regulatory oversight. That is, we recommend that investigators adapt relevant aspects of the existing CFR governing the protection of human subjects to studies of material from the dead where such study results provide information about living relatives. Specifically, we recommend that the use of tissue from deceased persons be reviewed through the formalized system for reviewing studies of living human beings.

Although full IRB review may not be necessary in all cases, studies proposing to use such materials should be reviewed by an IRB chairperson or other institutional official responsible for complying with the federal regulations [45 CFR 46 1996]. This review would determine if the research should be in the "exempt" category and, if not, what methods of reducing risk ought to be employed. The IRB chairperson, or other appropriate individual, should also determine whether the proposed research may have implications for surviving relatives of the deceased subject. If this is the case, the project should undergo full review by the IRB. The investigator should outline the risks involved in the project and propose an appropriate consent process. When using identifiable samples from living subjects, researchers should consider the effects their research might have on relatives. Investigators and IRBs must be aware that research on stored samples from dead subjects can have implications similar to those of living persons. The IRB can then determine the appropriateness of the study and the mechanisms to protect persons who may be exposed to the risks, as is currently done for studies of living persons.

Although the added safeguards we advocate will require some time and effort, this increased review process may not be burdensome. Further, the additional review will benefit the relatives of the deceased individuals whose specimens were studied and enhance the public's trust of the research enterprise. The issue of balancing the inconvenience and expense of a research project against the requirement to protect human subjects is clearly addressed in the Belmont Report [National Commission for the Protection of Human Subjects, 1979]. The report states that "Care should be taken to distinguish cases in which disclosure [of risks]

would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator." This "inconvenience" is interpreted to include time and expense involved in research execution, as these difficulties would not destroy or invalidate the research.

Good science requires sound planning and design. Regulations and codes of ethics are written to ensure minimal standards of conduct. The specification of minimal standards does not presume that they will be adequate in all situations. Molecular genetics research is an area in which scientific progress has overtaken the regulatory process. Adjustments to procedures, and ultimately to policies and regulations, are necessary. However before policy and regulatory changes take place the scientific community can take the leadership role in adjusting its own procedures to optimally protect persons involved in research. The process of broad and knowledgeable IRB review enables high standards in the conduct of genetics and molecular biologic research. Thorough review of written proposals describing the ethical aspects of a genetics study involving samples from dead persons ought to be standard practice regardless of what is required by regulation. The scientific community should set high standards of conduct and be willing to revise those standards when new processes or problems demand reassessment of the status quo.

The status quo concerning use of samples from the dead in genetic and other molecular biologic studies is no longer adequate. A reevaluation of the risks and appropriate safeguards is necessary because of technological advances. A review consistent with 45 CFR 46 meets this newly emerging need by providing increased protection to the relatives of deceased individuals whose samples are used for genetics research. In addition, it demonstrates to the public that researchers take seriously their responsibilities to protect persons from research risks, regardless of the source of such risks.

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